NEUROPHYSIOLOGICAL ESTIMATES OF HUMAN PERFORMANCE CAPABILITIES IN AEROSPACE SYSTEMS

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The effects of 4.5, 6.0 and 7.0 +Gz acceleration levels on the EEG were collaboratively studies with the USAFSAM. At no time did the EEG records suggest a significant impairment of cerebral functions. To achieve a separation of muscle and brain signals required development of new filtering methods which resulted in a capability for direct monitoring of brain function during severe physical stress in performing subjects. The need for adequate monitoring of diving performance ability resulted in the design of a new

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system using return-current density techniques. A wide range of studies have been conducted on cellular behavior in the visual system, in conditions of sleep and wakefulness, anesthesia, and as a concomitant of saccadic eye movements. Several studies were conducted on the unrestrained chimpanzee including sleep-wake cycles. Important studies on the effects of electromagnetic fields on CNS and behavior were conducted. Pattern recognition techniques were developed. Specific details are presented in the 32 papers published in the open scientific journals.

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SECTION I

ESTIMATES OF HUMAN PERFORMANCE AND RELATED STUDIES IN MONKEYS

INTRODUCTION

This Final Report on AFOSR Contract No. F44620-70-C-0017 covers the period October 1, 1969 through September 30, 1974.

The activities have covered a wide range of human performance measures and research on physiological mechanisms underlying these measures.

The report is presented in six sections:

1. Estimates of human performance
2. Cellular physiology
3. Biochemistry
   a) metabolic and endocrine chronobiology
   b) cerebral neurochemistry
4. Effects of weak electromagnetic fields on CNS and behavior
5. Computer analysis techniques and mathematical modeling
6. Bioengineering developments

1. Changes in the Electroencephalogram (EEG) during Sustained +Gz Acceleration

The effects of acceleration on the human body are determined by its magnitude, direction and duration. Man's capacity to endure these stresses sets the boundary conditions for the flight system in which he may be carried, either as a passenger, or more importantly, as a decision-maker in charge of high performance flight vehicles. His capacity to perform at a high level is degraded by accelerations substantially short of those producing actual tissue damage, primarily due to modified cardiopulmonary functions that lead in turn to impaired cerebral circulation.

In collaboration with the School of Aviation Medicine, Brooks Air Force Base, we investigated the effects of +Gz acceleration on the electroencephalogram, using acceleration levels of 4.5, 6.0 and 7 +Gz (Berkhout, O'Donnell and Leverett, 1973). Bilateral parieto-occipital EEG leads were recorded, together with EKG, before, during and after acceleration. Autospectral analyses of the EEG records were performed at the UCLA Health Sciences Computing Center.

Transient changes in the EEG records were noted during acceleration, at the peak and during deceleration. In most subjects these involved increased power at theta (4-7 Hz) and alpha (8-13 Hz) frequencies. Theta band activity is associated with emotional arousal and high levels of alertness (Walter, Kado, Rhodes and Adey, 1967), and its occurrence here is interpreted as a normal physiological response. This is supported by the finding that in some subjects, theta activity increased with increasing G loads, but declined at the peak of the stress, apparently in anticipation of decreasing physical demands thereafter. However, at no time did the EEG records suggest a significant impairment of cerebral functions. Post-acceleration records showed no abnormalities.

Detection of useful signals directly from the brain during these severe physical stresses is technically difficult. No signals may be visible in the original records, since the tiny brain signals are usually totally obscured by larger potentials from scalp and jaw muscles.

To achieve a separation of muscle and brain signals required development of new filtering methods (O'Donnell, Berkhout and Adey, 1974). First, the frequency distribution of the power in muscle signals (EMG) was determined. EMG signals were recorded from the biceps and from two craniofacial muscles (frontalis and masseter). Spectra of contracting frontalis and masseter muscles showed peak power between 30 and 60 Hz, with peak biceps power during contraction centered around 50 Hz. Over the course of sustained contraction, the proportion of power below 40 Hz increased in all 3 muscles. During contraction of the craniofacial muscles, EEG power increased at all points on the scalp. However, these increases were minimal below 14 Hz unless an EEG electrode was located directly over a contracting muscle. Using coherence calculations, which measure shared activity between different recording sites, increased coherence was observed only at frequencies above 14 Hz.

These results indicate that there is very little direct, linear EMG infiltration of the EEG signal below 14 Hz during tonic muscular contraction, unless the EEG electrode is extremely close to the contracting muscle. The results are most encouraging in showing a capability for direct monitoring of brain function during severe physical stress in performing subjects; a new capability attributable to modern monitoring and analysis techniques.

2. Underwater Monitoring of EEG in the Performing SCUBA Diver

The importance of electrophysiological correlates of performance under conditions that allow natural behavior of the subject in his working environment has been well documented. The extension of monitoring to stressful environments remote from the laboratory has been virtually limited to locations in which electromagnetic carrier waves may be used. The ocean presents new challenges for biotelemetry, because transmission of signals is poor except at ELF (below 100 Hz).

The need for adequate diver monitoring, with sensitive assessment of performance ability, led us to design and evaluate a novel system, using return-current density (RCD) techniques (Zweizig, Adey, Hanley, Hahn, Pilmanis, Given and Cockett, 1972). RCD transmission, when used in a frequency-modulated system, with data constituting a phase term in the carrier sinusoid, offers a workable method for underwater transmission of EEG signals. A frequency modulated carrier between 400 Hz and 300 KHz suffers little deterioration from natural electrical noises in sea water if proper filtering is used.

The RCD system does not involve a radiated electromagnetic field in the Maxwell sense. Rather, it involves establishment of a stationary field between a pair of electrodes. With a gradient of 40 volts/meter between such an electrode pair separated by 1-5 meters, the field decreases to about 30 microvolts/meter at a distance of 25 meters.

Initial tests were performed in the Hydrolab Habitat at Freeport, Grand Bahama Island, located at a depth of 15 meters. The transmitter pack was attached to the diver's air tanks. It contained an amplifier capable of transferring 5 watts of carrier power to the ocean surrounding the diver, using a carrier frequency of 2300 Hz. Records from the left parietoccipital region showed well developed trains of rhythmic activity

at theta band frequencies (4-7 Hz) in the free-swimming state. Computer analysis showed a progressive increase in theta activity in the first 10 minutes of swimming. This theta band dominant activity contrasted sharply with well-developed normal alpha band (9 Hz) activity in the same subject in laboratory records.

More recent tests have utilized a 3 channel EEG transmitting system in medical student subjects, diving to 20 meters at USC Santa Catalina Island Marine Biological Station. They performed mental and written arithmetic, as well as relaxing in eyes-closed prone postures, and swimming actively. Again, as in the preliminary habitat tests in Hydrolab, theta activity was augmented.

Since swimming underwater has many of the attributes of weightlessness, it is notable that spaceflight EEG records from Astronaut Borman and Cosmonaut Nikolayev also showed increased power at frequencies below the alpha band in the first days of weightlessness.

To the best of our knowledge, these are the first reported studies of the EEG in performing, free swimming divers. The techniques would appear to have great potential value in medical monitoring.

Hippocampal, Hypothalamic and Lateral Geniculate EEG Activity during Visual Discrimination with Monkey.

Color vision is an important factor in flight personnel selection. Beyond problems of congenital defects in color vision, the search for optimal performance in control of aircraft, and in other sophisticated decision-making procedures based on visual displays, has emphasized the importance of color in display lighting.

We have therefore examined EEG activity in deep brain structures in

the monkey associated with recognition of colored visual stimuli, and with learned motor performances based on these displays (Moise and Costin, 1974). The monkeys were trained to recognize and press a red, green or white disc when all three were presented simultaneously in a random sequence of spatial positions. Correct responses were rewarded with food. EEG activity was recorded in the hippocampus, hypothalamus and lateral geniculate nucleus. The EEG records were examined by spectral calculations.

In addition to a search for "signatures" in the visual pathways, this study attempted to further clarify the role of the hippocampal EEG in motor function and task performance. Hypothalamic activity was reviewed because of its well known motivational functions and its links to the hippocampus and limbic system.

It was found that the EEG patterns in the hippocampus just prior to discriminative responses were significantly different from records before the task was presented, and from records just after task presentation. and from records preceding spontaneous key presses in the absence of the visual task. These altered hippocampal EEG signatures occurred over a wide frequency range from 4-24 Hz. Moreover, since the motor movements in the discriminative response and the spontaneous presses were the same, we conclude that the EEG in hippocampus and visual pathways immediately before a discriminative response reflects non-motor activity that may be related to arousal, or to anticipation of the outcome of the response, or to information processing. No differences were detected in these records between correct and incorrect responses.

SECTION II

CELLULAR PHYSIOLOGY

A wide ranging series of studies have been conducted on cellular behavior in the visual system, in conditions of sleep and wakefulness, in anesthesia, and in particular, as a concomitant of saccadic eye movements.

Visual perception of movement is clearly of primary biological importance, yet surprisingly little is known about the neurophysiological mechanisms that subserve it. There are many unsettled questions, relating to the apparent stability of the visual world during voluntary eye movements. Moving objects are perceived as moving by a brain function that distinguishes image motion on the retina occurring with object movement from that associated with active eye movement. We have studied the basis for this distinction.

It has been proposed that a "corollary discharge" somehow modifies the visual information in the central visual pathway during an eye movement. In this model, an efferent (oculomotor) discharge resulting in an eye movement would be accompanied by a concurrent central discharge into the visual system, this anticipating and counteracting changes in visual input resulting from eye movement. This self-regulating compensation would stabilize the visual environment in normal conditions of active eye movements. Psychophysical studies have shown a rise in visual threshold during saccadic eye movements, called "saccadic suppression".

a. Influence of eye movements on geniculostriate excitability in the cat.

Our studies have shown (Adey and Noda, 1973):

i) Retinal impulses from a quick displacement of the image induced by either a saccadic eye movement or an object movement reduce transmission of visual information through the lateral geniculate nucleus. This may be a mechanism for saccadic suppression. Saccadic suppression would then be independent of the corollary mechanism.

ii) Saccade-contingent extraretinal impulses, probably arising in the oculomotor system, enhanced the excitability of the visual cortex. This facilitation may be a manifestation of the corollary mechanism. Thus, the visual cortex could be one of the locations for oculomotor-visual integration.

b. Excitability Changes in Cat Lateral Geniculate Cells during Saccadic Eye Movements

By testing single unit responses during eye movements in chronically prepared cats (Noda and Adey, 1973, 1974) we found that the excitability of LGN cells to orthodromic volleys was markedly decreased. It was further shown that this was caused by impulses arising in the retina which was excited transiently by a quick displacement of the image during an eye movement. We propose that this may be a mechanism for saccadic suppression.

The firing probability of LGN cells to stimulation of the optic chiasm was evaluated during an eye movement by triggering a stimulator from the horizontal electrooculogram, and altering delays in the stimulus pulse. Effects seen in lit environments completely disappeared when the eyes moved in total darkness. This indicates that the decreased excitability was caused by impulses arising in the retina, where the ganglion cells would be excited transiently as the image of the grating was displaced by an eye movement.

c. Role of Retinal Ganglion Cells in Transmission of Information on Saccadic Eye Movements and Quick Target Motion

The foregoing studies clearly implicated retinal ganglion cell discharges in the transient depression of excitability at geniculate levels in the visual pathway during quick target movement and saccadic eye movement. We therefore studied the behavior of 223 retinal ganglion cells in 49 experiments in 15 cats (Noda and Adey, 1974).

We found that there were at least 3 classes of ganglion cells in the cat retina that differed in their discharge patterns relating to eye movements scanning a stationary grating pattern. One class of cells showed transient bursts to eye movements. A second class of cells showed sustained discharges in certain directions of gaze, reflecting local luminance. A third class showed both transient and sustained responses.

d. Excitability Changes in Visual Cortical Units in Freely Behaving Cats

Spontaneous and evoked unit activity was studied in the visual cortex of chronic cats in behavioral states of resting arousal, light sleep and rapid-eye-movement (REM) sleep. Most cells increased their discharge rates in the sequence from light sleep to resting arousal to REM sleep. For the remainder the sequence was either resting arousal - light sleep - REM sleep, or REM sleep - resting arousal - light sleep (Kasamatsu and Adey, 1974).

The behavior of cat visual cortical cells was studied in natural transitions of sleep and wakefulness, with special reference to phasic (or bursting) activity in REM sleep and wakefulness (Kasamatsu and Adey, 1973). We examined the relations between cell firing in the visual cortex and certain brief, spike-like EEG waves known as ponto-geniculo-occipital (PGO) waves. These are clearly identifiable in REM sleep and similar waves can be seen in wakefulness.

It was found that most cells recorded in cortex outside the visual area had a positive relationship to PGO waves, while no such correlates were found in the primary visual (striate) cortex.

e. Neuronal Activity in the Association Cortex of the Cat during Sleep, Wakefulness and Anesthesia

Spontaneous activity of single neurons in association cortex (middle

suprasylvian gyrus) of the cat was studied to determine general trends in firing patterns between adjacent cells in the same cortical region (Noda and Adey, 1973). There has been widespread speculation concerning possible conditions in which synchronized firing might occur, and thus be used as an index of increased or decreased information processing.

With behavioral shifts from wakefulness to slow wave sleep, 85 percent of the units decreased and 14 percent increased their firing rates. The activity levels during pentobarbital anesthesia in terms of discharge rates of neurons, were in no way comparable to any states of natural sleep and wakefulness. During slow wave sleep and pentobarbital anesthesia, a high correlation was observed in the temporal patterns of firing of two neighboring cells recorded simultaneously. The probability of concurrent appearance of long silent periods in the neuronal pair. With a shift from sleep to wakefulness, correlation of silent periods between units was reduced and there was decreased probability of correlated firings. In arousal and REM sleep, the neuronal pairs discharged quite independently and the temporal patterns showed minimal correlation. The probability of correlated firings then fell to chance levels.

SECTION III

BIOCHEMISTRY

a. Metabolic and Endocrine Chronobiology

b. Cerebral Neurochemistry

c. Cytochemistry and Ultrastructure

d. Immunofluorescence

(Additional research on cerebral neurochemistry relating to effects of weak electromagnetic fields is included under Section IV)

a. Metabolic and Endocrine Neurobiology

i) Sleep-wake Cycle of an Unrestrained Isolated Chimpanzee under Entrained and Free-Running Conditions

Circadian rhythmicity of the sleep-wake cycle and many other biological processes is well established. These biorhythms are of interest to the aerospace scientist in his role as medical biologist. We have investigated the central neurons and metabolic biorhythms of an unrestrained chimpanzee subjected to 30 days isolation, under entrained and free-running conditions (McNew, Burson, Hoshizaki and Adey, 1972).

The subject in this test was an immature, male chimpanzee, weighing 20 Kg. More than 1 year prior to the experiment, an array of cortical and subcortical EEG electrodes were implanted, together with electro-oculogram (EOG) and electromyogram (EMG) leads. The EEG leads were located in parietal, occipital and hippocampal cortex, and in the amygdala. The EMG was recorded from posterior neck muscles.

The animal was exposed to 12 hours of light and 12 hours of darkness for 10 days. followed by 10 days of continuous light, and finally a further 10 days with 12 hours of light and 12 hours of darkness.

Using the EEG patterns as a biorhythm index, the animal exhibited a 24.0 hour sleepwake cycle in the first and last 10 day epochs. During the period of isolation in continuous light, the mean duration of the circadian sleep-wake rhythm was 24.8 hours. The significantly longer free-running sleep-wake rhythm was attributable to the animal spending more time awake and in rapid-eye-movement (REM) sleep. The animal's sleep cycle during the sleep phase averaged about 100 minutes during both the entrained and free-running conditions.

ii) Micturition Patterns of an Unrestrained Chimpanzee under Entrained and Free-Running Conditions

As a further series of observations on the chimpanzee subject in the circadian rhythm studies, our attention was focused on possible changes in micturition rhythms during 30 days of isolation without restraint. Stressful situations have been reported to affect urine production in the chimpanzee and man, and urination occurs in monkeys while excited or frightened. Urine volumes and voiding times were recorded every hour, beginning 14 days prior to isolation, ending 6 days after isolation. A control test was run 2 months after isolation as a control (Hoshizaki, McNew, Sabbot and Adey, 1972).

A clear circadian micturition rhythm occurred with a voiding peak immediately after the subject woke. Maximum urine volumes were voided in the morning hours. Under conditions of 12 hours light/12 hours darkness, there was a 24 hour flow rhythm. This was prolonged to 24.8 hours during exposure to continuous light, but a possible 24 hour micturition rhythm also occurred during the exposure to continuous light.

Distorted rhythm patterns indicative of stress were seen during the adaptation period preceding isolation, and during the early days of isolation. As time passed, the curves came to resemble the controls. Urine volume data also indicated stress during the preisolation period, and decreasingly so in the succeeding periods of isolation. Surprisingly, a stress response also occurred in the 6 days after termination of isolation.

iii) Effect of a 30-Day Isolation Stress on Calcium, Phosphorus and other Excretory Products in an Unrestrained Chimpanzee

The excretory pattern in the same chimpanzee was observed over the 49 days of pre-(14 days) and post-(5 days) isolation, as well as for the

30 days of isolation, and for 10 days in the home cage (Sabbot, McNew, Hoshizaki, Sedgwick and Adey, 1972).

Urine samples were analyzed for volume, osmolarity, creatinine, creatine, urea-N, 17-hydroxy corticosteroids, vanillmandelic acid, calcium and inorganic phosphorus. One-way analyses of variance performed on the urinary excretion parameters showed all except creatinine excretion to vary significantly. The changes observed in calcium and phosphorus were highly significant.

For the 30 days of isolation, the calcium balance remained positive, while the phosphorus balance became negative after the first 10 days of isolation, and progressively more so as the isolation continued. During isolation of the calcium-to-phosphorus intake ratio (Ca/P) did not vary, while the Ca/P excretion ratios (urine, fecal, urine+fecal) progressively decreased. The data suggest that the calcium-to-phosphorus excretion ratio might serve as a physiological stress indicator of Selye's adaptation syndrome, in what he has described as the "period of resistance."

b. Cerebral Neurochemistry

Studies performed under the contract represent a coordinated attack on the role of divalent cations, specifically calcium and magnesium, in the excitability of cerebral neuronal membranes, and the concurrent interactions of these ions with certain amino acids (glutamic, gamma-aminobutyric (GABA) and taurine) which are putative neural transmitters in cerebral tissue.

The reasons for this approach transcended a concern for solutions to fundamental problems in neurochemistry, although this was also a clear goal. Our interests have been directed to the possible physical and chemical substrates of interactions of weak electromagnetic fields with brain tissue

phenomena discussed in detail in a following section, and relating to possible hazards to service personnel exposed to radio and radar fields. Our findings indicate that the finding and release of calcium ions in cerebral tissue is an extremely active phenomenon in the outer layers of the neuronal membrane surface, where recent studies have located a delicate fabric of glue-like glycoprotein material, or "fuzz". This fuzz is now known to be part of a sensing or transducing mechanism for weak chemical stimuli, including hormone molecules; it also exhibits a singular sensitivity to weak electric gradients along the cell surface and in the intercellular space. Modification of calcium ion binding appears to be an essential step in sensing both weak chemical and electrical events at the membrane surface. The glycoprotein sheath extends substantially beyond the classical membrane described by the lipid bilayer or plasma membrane, and this new membrane model is described as the "greater membrane."

a. Ultrastructure of the Brain Studied with Phosphotungstic Stains

A widespread distribution of substances in the extracellular compartment of brain tissue was clearly demonstrated by electron microscopy of sections stained with phosphotungstic acid (PTA) in aqueous solution at pH less than 1.5 (Meyer and Bystrom, 1972).

Selective staining of the exterior of plasma membranes suggests that the extracellular material is anchored to cell membranes by bonding interactions between protein and lipid moieties of the glycocalyx ("fuzz") and those intrinsic to the plasma membrane.

Most interesting is the greater amount of PTA positively noted on the exterior surface of plasma membranes at the commencement of the axon near the nerve cell body, also at nodes of Ranvier on myelinated nerve fibers, and at synaptic junctions. Equally challenging are the longitudinal membrane

specializations seen as selective PTA-stainings. These support new concepts that nerve cell membranes are organized as a patchwork of mosaic, with widely differing properties at different points on the cell surface.

b. Triggered Release of Calcium and Gamma-Aminobutyric Acid (GABA) from Cat Cerebral Cortex by Calcium Ions

As a first approach to the problem of the binding of calcium to the surfaces of cortical neurons, our previous studies had indicated that it lies at the surface of cortical nerve cells as a series of tiny granules (Tarby and Adey, 1968). It is apparently bound to the glycoprotein "fuzz" as focal aggregates along the membrane, and also appears as a thin line outlining the nerve cell membrane surface in light microscopy actions. This appearance is absent on neuroglial membranes. Neuronal cytoplasm is devoid of calcium staining, whereas neuroglial cytoplasm is diffusely stained.

With this preliminary information on its structural localization, we then studied aspects of its binding and mobility in cat cerebral cortex (Kaczmarek and Adey, 1973). A special technique was developed to measure calcium and amino acid exchange in the intact cortex of the awake cat by superfusion of these substances with radioactive labels in a small plastic well placed over the cortex.

It was found that calcium triggers its own binding and release in a highly non-linear fashion; binding of one calcium ion causes the building of many more and vice versa. The addition of small amounts of calcium to the fluid bathing cortical cells elicits a large release of bound calcium into the bathing fluid; and at the same time, the added calcium causes a release of the inhibitory transmitter substance gamma-aminobutyric acid (GABA).

Our interpretation of this striking and singluar capacity of calcium

ions to trigger their own release (a phenomenon not shared by magnesium ions also present in the environment of brain cells in similar concentrations) is that the binding with cell surface glycoproteins is in the category of a cooperative process. Cooperative interactions have recently become the focus of attention in the physical sciences and biology as the possible basis for whole classes of weak interactions previously considered as impossible, by reason of the weak trigger events which would be effective in evoking a chemical or physical process with enormously larger energy expenditure. A process of stimulus amplification is thus involved, which may be many orders of magnitude larger than the trigger event.

It is noteworthy that the U.S. Air Force played an historic role in the support of research which has led to the present interest in biological cooperative systems. Hecht in 1943 showed that the human eye can detect a single quantum of light, but the mechanism for this baffling sensitivity remained unknown. Visual research in the past two years has shown that by a cooperative process, a single quantum of light releases 85,000 calcium ions, representing an energy amplification of more than 5 orders of magnitude on the original stimulus.

Briefly, to behave cooperatively a system must be far from equilibrium, and be sustained in this metastable condition by energy supplied from without. In these circumstances, a very weak stimulus, which may be less than the thermal (KT) perturbations in the system, may be adequate to destroy the metastable condition, with a large release of energy. The classic studies of Katchalsky and of Prigogine have laid the foundations for models of cell membrane surface cooperativity, based on the numerous negative fixed charges characterizing the polymer sheets of glycoproteins.

c. Biophysical and Metabolic Bases of Cooling Effects on Cortical Membrane Potentials in the Cat

Further evidence of cooperative binding and release of cations from membrane surface glycoproteins was seen in the effects of both transient and prolonged cooling during intracellular recording in neurons and neuroglial cells in the cortex of the awake cat (Adey, 1974).

Neuronal and silent cell membrane potentials were recorded during focal cooling by 5-6C, wither transiently for 1 to 2 minutes or for 10 to 15 minutes. Effects were compared between the awake cortex and under pentobarbital general anesthesia. In the awake cortex, transient cooling depolarized neurons and neuroglial cells, by 1-2 mV/C. The findings suggest actions at common membrane sites in effects of cooling and general anesthesia. Raising topical calcium levels from the normal 2mM to 20mM blocked depolarization by transient cooling. Pentobarbital anesthesia blocked the effects of sustained cooling on neuronal and silent cell membrane potentials.

Step-like and progressive decreases in membrane potentials of cortical silent cells were seen during repeated cooling, and support cooperative thermal transitions. In other studies, Gulati and Reisen (1972) suggested that accumulation of sodium and potassium in smooth muscle follows a cooperative mechanism, based on a similar signoidal plot of steady state electrolyte content against external potassium concentration. Their model envisaged cooperativity between nearest neighbor building sites throughout the cytoplasm, with a critical temperature between 12 and 17C.

In our experiments, abrupt decreases in membrane potential were most frequently observed at the end of rapid cooling to about 35C, or during rewarming from transient cooling. Moreover, the prominence of the membrane

potential changes suggest the membrane, rather than the general cytoplasm, as the primary site for these possibly cooperative ionic exchanges.

d. Chemical and Electrophysiological Effects of Glutamate in Cat Cerebral Cortex

The efflux of labeled calcium and GABA was tested by the superfusion technique described above in the presence of added glutamate. As noted above, efflux of both substances is sensitive to increased levels of calcium, but insensitive to increased levels of GABA.

If, however, the cortex was first treated with 25mM glutamate, neither calcium nor GABA efflux was affected by added calcium, but GABA efflux was now considerably enhanced by added GABA.

Thus, glutamate appears to cause a powerful building of calcium to the membrane surface. The source of the added efflux of labaled GABA remains uncertain, but the findings support the view (discussed below) that much of this increased flow originates in neuroglial cells, rather than neurons, and that future work on the role of GABA in cerebral tissue should consider not only its well known action as a synaptic transmitter, but also a modulatory role ascribable to non-synaptic sources and sites of action.

e. Factors Affecting the Release of Taurine from Cat Cerebral Cortex, and its Role in Normal and Epileptic Cortex

The study of the cerebral role of taurine has taken special significance since the finding that repeated injections of this amino acid may abolish seizure activity induced by application of cobalt to the cerebral cortex of cats and mice. Taurine also reverses changes in amino acid composition that take place during severe epileptic activity in both these species. A potential role as an inhibitory transmitter substance has been ascribed to taurine, and although the net efflux from the cortex

is variable, under certain conditions it may exceed that of all other amino acids.

We have therefore tested the sensitivity of taurine efflux from cortex to calcium ion concentration, and to weak electrical stimulation, and during epileptic seizure discharges. Added calcium increased the efflux of taurine. Weak electrical stimulation or addition of either 25 mM taurine or 25 mM GABA also increased taurine efflux.

During seizure activity induced by superfusion of cortex with a low-calcium medium, taurine efflux rose and fell regularly, peaks in efflux often being correlated with seizures. The addition of taurine to the superfusion medium during seizure activity prevented further seizures and stopped the waves of taurine efflux. We conclude that taurine has a direct effect on cortical excitability, and that, in its interplay with calcium ions, it may be involved in the regulation and inhibition of seizure discharges in normal cortex.

SECTION IV

EFFECTS OF WEAK ELECTROMAGNETIC FIELDS ON THE CENTRAL NERVOUS SYSTEM AND BEHAVIOR

Classical views on transmission and transaction of information in brain tissue have been predicated on structural concepts originating in the neuronal doctrine of Waldeyer in the 19th century. Briefly stated, this doctrine admits of only one mode of neuronal operation: axonal conduction of impulses to synaptic terminals on the cell body or dendrites; a "synaptic effect" on the membrane of this secondary neuron; an altered state of excitability in this neuron; and thus a modified transmission of information down its axon to tertiary and subsequent neurons in the chain.

This concept specifically precludes from consideration a role for the intrinsic electric fields pervading the extracellular space in brain tissue as the EEG, nor does it consider the possibility of interactions in dendrodendritic contacts between neighboring neurons. The advent of intracellular recording in the 1940's emphasized only the large size of the membrane potential (approximately 70 millivolts) and the synaptic potentials (1-10 millivolts) and the consequent improbability of an action on the excitable membrane attributable to the far smaller fields of the EEG in the extracellular space. and the extremely weak tissue components of environmental electric fields. The latter are measured in fractions of a microvolt/cm of tissue, as much as ten orders of magnitude less than the electric gradient of 1 Kilovolt/cm associated with synaptic activation of the neuronal membrane.

Nevertheless, due in large measure to research over the past 8 years in this Laboratory substantially supported by this and preceding contracts with AFOSR, it has become clear that brain tissue is, indeed, sensitive to electric gradients in the range from less than 1.0 microvolt to 20 millivolts/cm, and that certain imposed fields of this magnitude are capable of producing behavioral, neurophysiological and neurochemical effects,

even though they are from 5 to 10 orders of magnitude below gradients associated with classical synaptic mechanisms.

The phenomena disclosed by these studies clearly bespeak a class of processes different from synaptic mechanisms, which involve a large energy release in the trigger events. The only realistic models of these low-level interactions so far available are based on cooperative interactions between the weak electric fields and fixed charges on the surface glycoproteins. As a first step in the transduction of these weak fields, the fixed charges must achieve a similar state in adjacent charges, a condition of coherence. A charged biopolymer sheet in this coherent condition is extremely sensitive to weak field perturbations, as pointed out by Schwarz (1970). The ensuing events substantially enlarge the trigger event in a process of membrane amplification.

As a first approach to the problem we tested the effects of weak oscillating elec gradients applied directly to the cortex on the efflux of calc GABA.

a. Changes in c and Transmitter Fluxes in Cortex Induced by Weak Applied Oscillating Electric Gradients

We have tested the effects of electric stimulation of cat cortex with gradients in the range of 20-60 mV/cm on the efflux of labeled GABA and calcium from the cortical surface (Kaczmarek and Adey, 1974). To produce a non-focal electric field through the brain, we used electrodes of agar in lucite cylinders 2.6 cm high and 1.0 cm in diameter, placed on the front and rear of the cerebral hemisphere. The stimulus train was 200 pulses/sec (1.0 msec duration), and the electric gradient resembled the natural EEG gradient recorded across a 1.0 mm dipole.

This weak gradient produced highly consistent increases in efflux

of both calcium and GABA. There was a mean increase of 1.29 times for calcium and 1.21 for GABA. If these weak fields exerted their action through classical processes of transmitter release from synaptic terminals, important questions arise. For a typical synaptic terminal 9.5 μm in diameter, the extracellular gradient imposed by these fields is, at most, 2.5 microvolts across the terminal. Classic synaptic physiology offers no satisfactory explanation of how such a weak stimulus may affect the transmembrane potential of 50 millivolts sufficiently to influence transmitter release. Similar considerations apply to the effects of the fields on postsynaptic excitability, in which case a transmembrane potential of several millivolts as required to induce a change in activity. This change is equivalent to a gradient of 1 Kilovolt/cm across the membrane and is greater than the extracellular applied gradients by a factor approaching 10^5.

From the magnitude of the chemical changes induced by these weak applied gradients, we concluded that there is strong evidence favoring direct electrical interaction between cortical cells, based on the electric field components bathing their cell surfaces, and to which they contribute in the cellular genesis of the EEG. At the same time, the findings raised possibilities that even weaker interactions might occur with far weaker electromagnetic fields of natural and artificial origin in the immediate environment of the head.

b. Effects of ELF and Modulated VHF Fields on Brain Electrical Rhythms and Behavior

Prior to and concurrently with the above studies on weak electrical stimulation, we had performed an extensive series of behavioral and neurophysiological studies on the effects of weak ELF and modulated VHF fields

in man and animals, beginning in 1966.

Summarized briefly, it was shown that a small (5msec) reduction in a simple reaction time of approximately 200 msec occurred in 59 human subjects exposed to sine wave electric fields at 56-15 Hz and with gradients of 2 to 10 volts/meter (Hamer, 1968). This study led to a more elaborate investigation of estimates of the passage of time (5 sec) in monkeys exposed to 7-10 Hz fields at 10 volts/meter (Gavalas, Walter, Hamer and Adey, 1970). It was shown in 3 monkeys trained, extinguished and retrained in this paradigm that a reduction in the estimate of 5.0 sec by 0.3 - 0.5 sec was a consistent effect in either initial training or retraining in the presence of the 7.0 Hz, 10V/meter field. The 10 Hz field at the same intensity was without effect. In extensive subsequent studies, which are still continuing, Dr. Gavalas-Medici has shown that there is a threshold for these effects, with maximum sensitivity at frequencies between 5 and 10 Hz, where the threshold is between 1 and 10 volts/meter. At frequencies of 45, 60 and 75 Hz, the threshold is much higher, around 50 volts/meter. In the course of daily 4 hour exposures to the test fields, it was found that a slowly progressive entrainment of the EEG occurred at the 7 Hz field frequency in the hippocampus, a structure characterized by a strong tendency to 7 Hz rhythms and also apparently involved in estimates of the passage of time. A highly significant aspect of these studies was the measurement in collaboration with the Illinois Institute of Technology Research Institute, of the total current in a phantom monkey head exposed to these fields at 0.8 nanoamp, with a probable range of electric gradients in the brain tissue between 0.1 and 0.01 microvolts/cm, approximately 10 orders of magnitude below the level of the classic synaptic gradient.

i) Effects of Modulated VHF Fields on Specific Brain Rhythms in Cats.

As a departure from the rise of ELF fields, we initiated the use of a 147 MHz VHF field amplitude modulated at EEG frequencies (0.5 to 30 Hz). It was anticipated that the induced electric gradient in the tissue with an incident field of 1.0 milliwatt/cm^2 would be in the range of 100-300 microvolts/cm and that, although the tissue would not "see" the VHF carrier the amplitude modulation would be demodulated by the numerous phase partitions in the tissue, particularly membrane surfaces associated with biopolymer sheets having a fixed charge structure and marked charge asymmetry, as described above. In many respects these systems would be expected to exhibit properties resembling a semiconductor.

We have exposed cats to 147 MHz fields with an incident energy of 1.0 mW/cm^2 or less and amplitude modulated at biological frequencies of 1 to 25 Hz. The animals were restrained in a hammock, with the longitudinal axis of the body kept parallel to the field plates.

Our series of these cats was operantly trained to produce specific transient brain rhythms following presentations of a light flash stimulus at 30 sec intervals. Levels of performance in this task were tested by visual inspection of records and by spectral analysis during conditioning and extinction of the response. For some animals this sequence of conditioning and extinction was carried out in the presence of the VHF fields, amplitude modulated at the same frequency as the specific brain rhythm or "signature". Other animals in this series were treated as controls, and were trained and extinguished in the absence of the VHF fields. The irradiated animals differed markedly from the controls. Their rate of performance was higher, the spectral bandwidth of the elicited EEG response

was narrower, and they showed a remarkable resistance to extinction of the response (in the absence of any punishment for failure to respond). The extinction of the response took a minimum of 50 days during irradiation, compared with a mean of 10 days without VHF fields.

The specificity of the frequency of the modulation was tested on another group of cats. Their spontaneous transient EEG patterns were used to trigger the VHF fields for 20 sec. It was found that the fields acted as reinforcers (increasing the rate of occurrence of spontaneous rhythms) only when modulated at frequencies close to the biologically dominant frequency of the selected intrinsic EEG rhythmic episodes.

We conclude that there are clear interactions between mammalian brain tissue and weak VHF electromagnetic fields, contingent upon the modulation of the field in the range of naturally occurring brain rhythms, since unmodulated fields were uniformly without effect. The precise upper limit of the effective modulation frequencies remains to be determined, but it may be noted that French and Soviet workers have compared CW and pulsed microwave fields and observed effects attributable to modulation at pulse repetition frequencies as high as 700/sec, and an absence of effects of unmodulated fields with the same average incident energy.

iii. Altered Calcium Bindings in Isolated Brain Tissue Exposed to Modulated VHF Fields

These findings attributable to modulated VHF fields supported that a critical experiment might be performed with isolated brain tissue, exposing it to modulated VHF fields and observing the binding and release of calcium (Bawin, Kaczmarek and Adey, 1974).

Isolated chick brains were first equilibrated with a physiological

medium containing labeled calcium, and the efflux into the bathing medium measured. The tissue was then exposed to the VHF fields at modulation frequencies from 0 to 30 Hz. The unmodulated fields were without effect, but a remarkable "timing curve" was observed at modulation frequencies between 10 and 25 Hz. Modulation of the VHF field between these frequencies produced a smoothly rising and falling curve of increased calcium efflux, and a return to control levels above and below those modulation frequencies. Moreover, the effect persisted after initial metabolic poisoning of the tissue with 10^{-4}M potassium ganide, which, however, does not interfere with membrane surface fixed charge structure (as shown by Elul, 1966, 1967, in our previous research supported by AFOSR). Also, striated muscle remained unresponsive in identical exposures.

Thus, the findings appear to make a further important link in the chain from overt behavior to molecular biology of the membrane sensing and transducing of weak electric field influences. They emphasize the binding and release of calcium to surface polyanions as an integral phenomenon.

SECTION V

COMPUTER ANALYSIS TECHNIQUES AND MATHEMATICAL MODELING

1. Pattern Recognition Techniques Applied to EEG and other Physiological Data

We have continued the development of pattern recognition techniques, including "fuzzy clustering" and a comparison of this method with other techniques pioneered in the Laboratory, including stepwise and non-stepwise discriminant analysis (Ruspini, 1972). The findings have emphasized the value of these methods in detecting subtle patterns in the EEG, quite undetectable by visual inspection, but having great value in signaling of changing states during decision-making and high levels of alerted performance. It is also clear that no single method of pattern recognition is uniformly successful in handling all types of EEG data correlated with behavioral performances (Larsen et.al., 1972).

2. Effects of Auditory Stress on High Demand, Decision-Making Performance

We have examined the effects of auditory stress on non-human primates performing demanding, complex information processing tasks. The goal is to provide behavioral and neurophysiological models that may be valid in extrapolation to man performing complex tasks under auditory stress. The test monkeys have been implanted with cortical and subcortical electrodes. The auditory stressors include prerecorded noise from aircraft and airfield operating environments, as well as graded intensities of white noise and sharp reports.

We have developed computing hardware and software for sophisticated evaluation of neurophysiological and behavioral performance data in a number of tasks in which information handling demands can be easily varied (Moise, 1974a). The tasks used in testing the animals focus on the kinds of processes often used by humans when short-term information-handling and decision-making is required (e.g. registration of information, moment-

to-moment recall from memory, decision-making between alternatives on the basis of recalled data). Analysis of sequential properties of these behaviors has been facilitated by development of a powerful technique for systematically examining substrings of sequentially ordered data (Nirenberg, Haber and Moise, 1973). The technique has shown that there are facilitating and degrading influences of immediately preceding stimulus configurations on correct performance of any given trial in a delayed-matching task.

Continuous noise from the cockpit of a B-52 bomber at approximately 90db, or continuous noise at 4, 10, 40 and 400 Hz were presented to animals performing a delayed-matching task (as an initial training paradigm A semi-implantable biotelemetry system was developed for acquisition of EEG and eye movement data.

These initial data have been examined for effects of initiation and termination of noise, and of continuous noise on behavior and performance (Moise and Costin, 1974b). Continuous presentation of noise was clearly stressful to the animals, as evidenced by increased behavioral agitation. Analysis of performance data revealed little overall effect on task performance but suggests that low frequency (4 Hz) noise may improve performance in some animals. Comparison of noise vs. non-noise conditions revealed different effects on the visual system (in lateral geniculate bodies and optic cortex) depending on the frequency of auditory stimulation.

SECTION VI

BIOENGINEERING DEVELOPMENTS

1. Biomedical Telemetry
2. Underwater Biotelemetry
3. Automated Behavioral Test Procedures

1. Biomedical Telemetry

a) An Eight-Channel Micropowered PAM/FM Biomedical Telemetry System

The advent of multichannel personal biotelemetry systems in the late 1960's, many of which were pioneered in this Laboratory, opened new opportunities in personnel monitoring in operational environments and in medical evaluation of neurological and cardiovascular disorders. Our initial multichannel systems used FM/FM and FM/AM techniques.

Primarily with the support of AFOSR, we have developed a microminiature, micropowered digital system rising pulse amplitude modulation (PAM). Recent advances in complementary symmetry metaloxide semiconductor (CMOS) techniques of integrated circuit construction offer major savings in power consumption, allowing high performance linear amplifiers with low noise characteristics to be operated with currents in the 15-20 microampere range.

An 8-channel biotelemeter using these techniques was constructed on a ceramic mother-board disc, and included a signal conditioner, multiplexer, and transmitter (Olsen, Firstenberg, Huston, Dutcher and Adey, 1971). The disc is 6.35 cm in diameter and 0.97cm thick. The amplifier design uses three Fairchild A735 operational amplifiers in a differential configuration, which provides extremely high input impedance (30 mgohms or more) and a common mode rejection at 100 Hz in excess of 95db. The PAM multiplexer is noteworthy for its simplicity of design, using only 4 integrated circuits: two RCA CD 4016 four channel analog switch circuits, four dual input gates (RCA CD 4001D), two of which form a multivibrator for the timing signal, and an RCA CD 4017 decade counter. Each input gate is sampled 256 times per sec, which is adequate for the 100 Hz bandwidth.

The transmitter uses a Vackar self-controlled oscillator, selected after extensive testing of the Clapp and Seiler circuits.

We have evaluated units of this type in intensive care wards, in operating room monitoring and in cardiac critical care patients. They are remarkable for their robustness and reliability. We have applied our earlier FM-FM and FM-AM systems, which retain the very desirable characteristic of allowing unlimited transmission of the received multiplexed subcarriers on voice grade telephone lines in a wide variety of telemedicine applications, or permanent acquisition on simple analog recorders.

b) An Eight-Channel Semi-Implantable Telemetry System for Animal Research

Obtaining physiological data from unrestrained and uncooperative animals requires packaging techniques that, irrespective of circuit design, is an art in itself. This is particularly true in subhuman primates, which have highly manipulative hands capable of destroying even the most carefully designed telemeter. Nevertheless, there are singular advantages in many animal studies in having freeranging subjects, unencumbered by wire connections.

We have therefore repackaged the PAM system described above to permit its implantation in a receptacle on the dental acrylic implant attached to the skull of monkeys and chimpanzees for CNS and CV research (Olsen, Moise, and Huston, 1974).

The amplifiers, multiplexer and transmitter are packaged as separated welded cordwood modules which, by using flatpack ICs, 1/8 watt resistors and miniature capacitors, are made quite small. The modules are mounted on a miniature printed circuit board along with the four mercury cells that provide the power. The total assembly of 6.8 cm by 3.6cm by 1.7 cm, and weighs 54 gm, including batteries (Fig. 1). The inverted

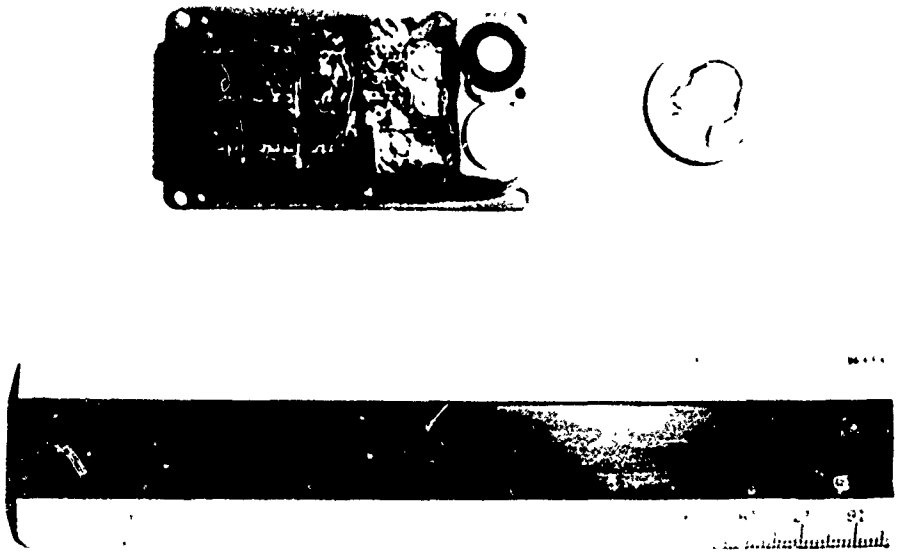

FIGURE 1

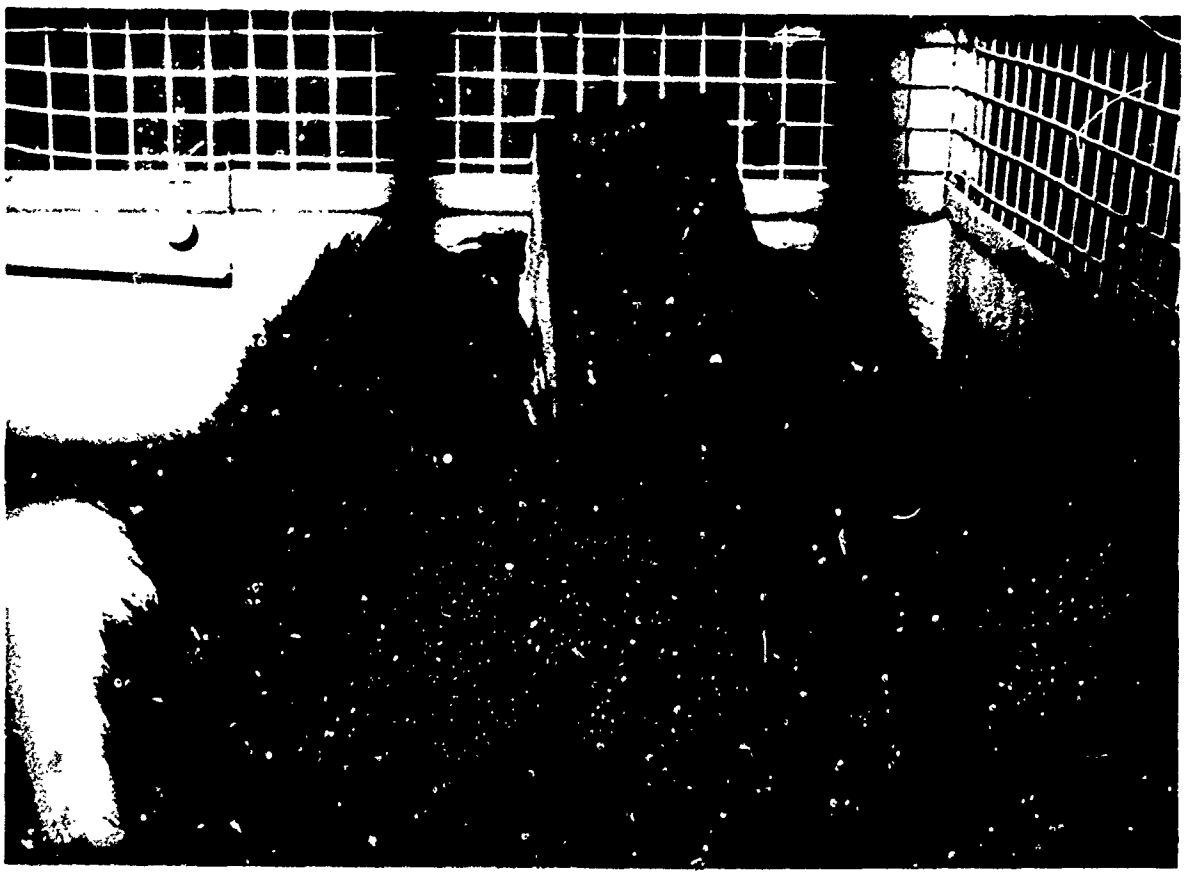

FIGURE 2

assembly (printed circuit side up) mounts in a lucite receptacle which is attached to the monkey's skull with dental acrylic (Fig. 2). At one end of the receptacle is an 18 pin strip connector which mates with a corresponding connector at one edge of the printed circuit board.

This system is ideally suited to simultaneous studies in a colony of unrestrained animals.

2. Underwater Biotelemetry

Reference is made here to the return-current-density (RCD) biotelemetry system described above in this report in its application to ocean scuba diving with monitoring of the EEG.

The engineering design of this system was the primary responsibility of R.J. Zweizig, and its packaging and system checkout was performed by P.M. Hahn in collaboration with John Hanley, M.D. from our Laboratory. We are deeply indebted to Dr. A. Pilmanis and Dr. R. Given of the USC Dept. of Physiology and the USC Marine Biology Station at Catalina Island for their patient help in making test dives and in instructing others in the use of the biotelemetry system.

3. Automated Behavioral Test Procedures

We have developed a flexible hardware/software system for use with a PDP8-1 computer for conducting research in behavioral neurophysiology (Moise, Olsen and Huston, 1974). A real time monitor was designed to facilitate development, debugging and modifications of programs to run experiments. It relieves the programmer of the burden of dealing with hardware dependent functions such as interrupt handling and input/output. In addition it provides the user with a large library of "callable" routines to perform functions commonly needed in conducting experiments.

The monitor is modular in design and can be expanded or modified for use with many configurations of the PDP-8 family of computers.

The system has the capacity to 1) act as a task controller for a large number of experimental paradigms (operant conditioning to complex design making behavior), 2) collect behavioral data in a well-organized format for subsequent analysis, 3) monitor and record physiological data (EEG, EKG, EMG,etc) for on-line analysis during the experiment and 4) permit computer control of a potentially large number of experimental parameters (i.e. brain stimulators, noise generators, house lights, etc.)

The computer is an 8K PDP-8/I with a 1.66 million word disc, 7 and 9 track magnetic tape drives, 64 channel analog-to-digital converter, 8 channel digital-to-analog converter, 12-bit relay buffer, teletype, and experimental apparatus interface.

BIBLIOGRAPHY

1. Adey, W.R. 1974 Biophysical and metabolic bases of cooling effects on cortical membrane potentials in the cat. Exper. Neurol. 42:113-140

2. Adey, W.R. 1975 Evidence for cooperative mechanisms in the susceptibility of cerebral tissue to environmental and intrinsic electric fields.

3. Adey, W.R., and Noda, H. 1974 Influence of eye movements on geniculostriate excitability in the cat. J. Physiol. London 235:805-821

4. Bawin, S.M., Gavalas-Medici, R.J., and Adey, W.R. 1973. Effects of modulated very high frequency fields on specific brain rhythms in cats. Brain Research 58:365-384

5. Bawin, S.M., Kaczmarek, L.K., and Adey, W.R. 1975. Effects of modulated VHF fields on the central nervous system. Ann. New York Acad. Sci., in press.

6. Berkhout, J., O'Donnell, R.D., and Leverett, S. 1973. Changes in electroencephalogram spectra during repeated exposure to +Gz acceleration. USAF Aerospace Medical Laboratory, Wright Patterson Air Force Base, Document AMRL-TR-72-123.

7. Elul, R. 1966. Use of non-uniform electric fields for evaluation of the potential difference between two phases. Trans. Faraday Soc., London 62:3484-3492.

8. Elul, R. 1967. Fixed charge in the cell membrane. J. Physiol., London 189:351-365

9. Gavalas, R.J., Walter, D.O., Hamer, J., and Adey, W.R. 1970. Effect of low-level, low-frequency electric fields on EEG and behavior in Macaca nemestrina. Brain Research 18:491-501

10. Hoshizaki, T., McNew, J.J., Sabbot, I., and Adey, W.R. 1972. Micturition patterns for an unrestrained chimpanzee under entrained and free running conditions. Aerospace Med. 43:149-154

11. Kaczmarek, L.K., and Adey, W.R. 1973. The efflux of $^{45}Ca^{2+}$ and ^{3}H-gamma-aminobutyric acid from cat cerebral cortex. Brain Research 63: 331-342

Bibliography (cont'd)

12. Kaczmarek, L.K., and Adey, W.R. 1974a. Weak electric gradients charge ionic and transmitter fluxes in cortex. Brain Research 66: 537-540.

13. Kaczmarek, L.K. and Adey, W.R. 1974b. Factors affecting the release of 14C-taurine from cat brain: the electrical effects of taurine on normal and seizure-prone cortex. Brain Research 76: 83-94.

14. Kaczmarek, L.K. and Adey, W.R. 1974c. Some chemical and electrophysiological effects of glutamate in cerebral cortex. J. Neurobiol. 5:231-241

15. Kasamatsu, T., and Adey, W.R. 1974. Excitability changes in various types of visual cortical units in freely behaving cats. Physiology and Behavior 13:101-112.

16. Kasamatsu, T., and Adey, W.R. 1973. Visual cortical units associated with phasic activity in REM sleep and wakefulness. Brain Research 55: 323-331.

17. Larsen, L.E., Ruspini, E.H., McNew, J.J., Walter, D.O., and Adey, W.R. 1972. A test of sleep staging systems in the unrestrained chimpanzee. Brain Research 40:319-343.

18. McNew, J.J., Burson, R.C., Hoshizaki, T., and Adey, W.R. 1972. Sleep-wake cycle of an unrestrained isolated chimpanzee under entrained and free-running conditions. Aerospace Med. 43:155-161.

19. Moise, S.L., Olsen, D.E., and Huston, S.W. 1974. An automated system for primate instruction for behavioral neurophysiology.

20. Moise, S.L., and Costin, A. 1974a. Hippocampal, hypothalamic and lateral geniculate activity during visual discrimination in the monkey. Physiology and Behavior 12:835-841.

21. Moise, S.L., and Costin, A. 1974b. Effects of auditory stress on high demand decision making behavior in the monkey. USAF Contractors Conference, Brooks AFB, September 1974.

22. Nirenberg, L.M., Haber, J., and Moise, S.L. 1973. A high speed algorithm for computing conditional probabilities of substrings of sequentially observed data. Behavior Research Methods and Instrumentation 5:291-294

Bibliography (cont'd.)

23. Noda, H., and Adey, W.R. 1973a. Neuronal activity in the association cortex of the cat during sleep, wakefulness and anesthesia. Brain Research 54:243-259

24. Noda, H., and Adey, W.R. 1973b. Excirability changes of lateral geniculate cells following saccadic eye movements in cats. Proc. Soc. for Neuroscience. Third Annual Meeting.

25. Noda, H., and Adey, W.R. 1974a. Retinal ganglion cells of the cat transfer information on saccadic eye movement and quick target motion. Brain Research 70:340-345

26. Noda, H., and Adey, W.R. 1974b. Excitability changes in cat lateral geniculate cells during saccadic eye movements. Science 183:543-545

27. O'Donnell, R.D., Berkhout, J., and Adey, W.R. 1974. Contamination of scalp EEG spectrum during contraction of craniofacial muscles. Electroenceph. clin. Neurophysiol. 37:145-151

28. Olsen, D.E., Firstenberg, A., Huston, S.W., Dutcher, L.R., and Adey, W.R. 1971. An eight channel micropowered PAM/FM biomedical telemetry system. Inst. Electrical Electronics Engineers, National Telemetering Conference, Washington, D.C. 4pp.

29. Olsen, D.E., Moise, S.L., and Huston, S.W. 1974. An eight-channel semi-implantable telemetry system for animal research. Proc. Internat. Telemetry Conference, Davos, Switzerland 4 pp.

30. Ruspini, E.H. 1972. New cluster analysis techniques; fuzzy and probabilistic clustering and some of their applications. Proc. Fifth Hawaiian Conference on System Science, Honolulu pp. 186-188

31. Sabbot, I.M., McNew, J.J., Hoshizaki, T., Sedgwick, C.J. and Adey, W.R. 1972. Effect of a 30-day isolation stress on calcium, phosphorus and other excretory products in an unrestrained chimpanzee. Aerospace Med. 43:142-148

32. Zweizig, J.R., Adey, W.R., Hanley, J., Hahn, P.M., Pilmanis, A.A., Given, R.R., and Cockett, A.T.K. 1972. EEG monitoring of a free-swimming diver at a working depth of 15 meters. Aerospace Med. 43:403-407